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(56) Documents cited
GB 1511302
GB 1444621
GB 1442154
GB 1399888
GB 1219884
GB 698864
GB 475291
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(54) **Amino acid solutions for patients with cancers**

(57) This invention provides an amino acid solution for a patient with a cancer comprising essential amino acids, characterized in that the solution does not contain methionine which is a kind of essential amino acid; and a method of nourishing a patient with a cancer characterized by giving the patient the amino acid solution.

The essential amino acids are leucine, valine, isoleucine, lysine, phenylalanine, threonine and tryptophan. The solution may also contain at least one nonessential amino acid selected from arginine, histidine, glycine, alanine, aspartic acid, glutamic acid, proline, serine, tyrosine and ornithine; starch, sucrose, glucose, maltose, fructose, sorbital, xylitol, ascorbic acid, nicotinic acid, pantothenic acid, thiamine, riboflavin, pyridoxine, menadione, biotin, folic acid, vitamin B12, inositol, sodium bisulphite and/or phosphoric acid. The solution may be administered in conjunction with known anti-cancer agent(s) e.g. Mitomycin C, 5-fluorouracil and neocarzinostatin.

GB 2 029 220 A

SPECIFICATION

Amino acid solutions for patients with cancers

This invention relates to amino acid solutions for patients with cancers.

When it is impossible to orally or intestinally give nourishment to a patient postoperatively, for example, the patient is usually nourished by parenteral or non-intestinal nutrition for the maintenance and improvement of the physical fitness. For this purpose, amino acid solutions of various compositions are known and widely used.

Such known amino acid solutions, which are inherently intended for parenteral nutrition, are basically all alike in amino acid composition, simulating human milk, chicken eggs, human serum albumin, etc. which contain the amino acid nutrients essential to the human body. Accordingly the solutions incorporate all the eight essential amino acids as indispensible components.

In the couse of research on amino acid solutions especially useful for patients with cancers, we have unexpectedly found the surprising fact that the known amino acid solutions, when not containing methionine, act to reduce cancer cells or suppress cancers while maintaining the effect of giving nourishment of the amino acids contained therein.

An object of this invention is to provide amino acid solutions having effects of inhibiting or reducing cancer cells and also affording nutrition.

Another object of the invention is to provide amino acid solutions which are usably conjointly with known anti-cancer agents to remarkably enhance the effect of the agents.

These and other objects of this invention will become more apparent from the following description.

In an amino acid solution comprising essential amino acids, the invention provides an amino acid solution for a patient with cancer characterized in that the solution does not contain methionine which is a kind of essential amino acid.

The amino acid solutions of this invention achieve the effects totally unexpected from the conventional amino acid solutions and the parenteral therapy with the use of such solutions, namely the effect of reducing cancer cells or anti-cancer effect and the attendant outstanding effect of affording an increased life-span while substantially assuring the maintenance and improvement of the physical fitness by the nutrition provided by the solution. The solutions of this invention, when used in combination with a known anti-cancer agent such as mitomycin - C, 5 - fluorouracil, neocarzinostatin or bischloroethyl nitrosourea, greatly enhance the effect of the agent. Thus the amino acid solutions of this invention act to reduce or inhibit cancer cells while producing any side effect whatever. The invention therefore also provides a useful method of treating cancers. The outstanding effects of the amino acid solutions of this invention are totally inconceivable from the known amino acid solutions because when administered to the cancer patient, the solution acts to maintain his physical strength by nutrition while also affording the nutrients to the cancer cells in the living body at the same time to assist in the growth of the cells. Consequently the parenteral nutrition merely retards the reduction in the body weight of the patient, failing to alleviate the symptoms or add to the body weight to any extent. In contrast, the solution of the invention not containing methionine acts to selectively inhibit the growth of the cancer cells in the living body, resulting in an increase in the body weight and regression of the symptoms.

The amino acid solutions of this invention can be similar to the aforementioned known amino acid solutions in composition, except that the present solutions are free from methionine. The composition of the present solutions is determinable as desired in accordance with the mode of administration, symptoms of the patient, period of administration, etc. Basically the present solutions comprise seven essential amino acids other than methionine, namely leucine, valine, isoleucine, lysine, phenylalanine, threonine and tryptophan. The solutions of this invention contain these essential amino acids preferably in the following proportions (g/liter).

Leucine	1.4-14.0 g/liter
Valine	1.4-10.0
Isoleucine	1.6-10.0
Lysine	1.5-14.9
Phenylalanine	1.0- 9.4
Threonine	1.0- 6.7
Tryptophan	0.4- 4.0

In addition to these seven essential amino acids, nonessential amino acids can be incorporated into the solutions of the invention. Examples of such dispensable amino acids are arginine, histidine, glycine, alanine, aspartic acid, glutamic acid, proline, serine, tyrosine, ornithine, etc., among which arginine, histidine and glycine are preferable to use. These dispensable amino acids, although usable in desired amounts, may be incorporated preferably in the following proportions (g/liter).

Arginine	0-13.2 g/liter
Histidine	0- 6.0
Glycine	0-18.0
Alanine	0- 5.0
Aspartic acid	0- 6.0
Glutamic acid	0- 9.0
Proline	0- 9.0
Serine	0- 6.0
Tyrosine	0- 2.0
Ornithine	0- 6.0

More preferably the amino acid solutions of the invention have the following amino acid composition. (The proportions are in g/liter).

Leucine	1.7-14.0 g/liter
Valine	1.7- 9.5
Isoleucine	1.8- 9.6
Lysine	1.5-14.7
Phenylalanine	1.0- 6.4
Threonine	1.3- 6.7
Tryptophan	0.4- 3.5
Arginine	1.0-13.2
Histidine	0.9- 3.0
Glycine	2.3-15.0
Alanine	0- 4.8
Aspartic acid	0- 2.5

Glutamic acid	0- 6.0
Proline	0- 2.3
Serine	0- 1.8
Tyrosine	0- 1.7
Ornithine	0- 5.0

The above-mentioned amino acids useful for the preparation of the amino acid solutions of the invention are preferably pure crystalline amino acids which may be of the D- or L-form or mixture thereof. However, the L-form is preferred. The amino acids are used usually in free forms but are not limited thereto; they are usable in the form of pharmacologically acceptable salts with acids such as hydrochloric acid, acetic acid and the like.

The amino acid solutions of this invention can contain, in addition to the foregoing amino acids, various additives which are usually used for solutions of this type, such as carbohydrates, vitamins, fats, electrolytes, antiseptics, stabilizers, etc. Examples of such additives are starch, sucrose, glucose, maltose, fructose, sorbitol, xylitol, ascorbic acid, nicotinic acid, pantothenic acid, thiamine, riboflavin, pyridoxine, menadione, biotin, folic acid, vitamin B_{12}, inositol, sodium bisulfite, phosphoric acid, etc.

The amino acid solutions of this invention, like known amino acid preparations, are usually sterile aqueous solutions and are given as infusion solutions parenterally or non-intestinally for example in the form of intravenous injections and drips. The solutions may be administered orally and enterally when possible. The dose can be determined suitably in accordance with the symptoms of the patient, etc. The solution can be given at a dose needed for nurishing the patient. The solutions are given usually at a daily dose of about 100 to about 1500 ml, preferably about 500 to about 1500 ml.

The anti-cancer agent to be used conjointly with the amino acid solution of this invention is given at a dose generally adopted although the dose can be determined suitably in accordance with the kind of the agent, type of the cancer, method of administration, etc. Various anti-cancer agents are usable singly or in admixture. For example, when 5-fluorouracil alone is to be given to a patient with gastric cancer in combination with the present solution, the agent is intravenously administered dropwise at a dose of 15 mg/kg/day for 5 consecutive days and thereafter at a dose of 7.5 mg/kg/day every other day, or is intra-arterially administered at a dose of 5 to 10 mg/kg/day for 10 to 20 days. Mitomycin-C, when to be used in combination with the present solution for a patient with gastric cancer, is given intravenously once or twice a week at a dose of 8 to 10 mg/kg each time.

The solutions of this invention are useful for patients for example with gastric cancer, carcinoma of the colon, cancer of the rectum, carcinoma of the esophagus, cancer of the pancreas, colangioma, hepatoma and various other cancers.

The invention will be described below with reference to examples, in which the values given in the parenthesis are the amounts of the amino acids used in the form of salts, calculated as free amino acids.

Example 1

The following amino acids are dissolved in sterile water in concentrations (mg/100 ml) described below to formulate an amino acid infusion solution of the invention. The solution prepared is sterilized at 110°C for about 10 minutes.

	mg/100 ml
Leucine	410
Valine	200
Isoleucine	180
Lysine HCl	620
	(496)
Phenylalanine	290
Threonine	180
Tryptophan	60
Arginine HCl	270
	(223.3)
Histidine HCl.$2H_2O$	130
	(88.7)
Glycine	340
Total amino acids	2680 mg/100 ml
Total free amino acids	2480 mg/100 ml
Total nitrogen	0.397 g/100 ml

Examples 2 to 6

In the same manner as in Example 1, amino acid infusion solutions of the following compositions are prepared according to this invention.

Composition (mg/100 ml)	*Example 2*	*Example 3*	*Example 4*	*Example 5*	*Example 6*
Leucine	410	410	1090	267	175
Valine	200	200	960	198	175
Isoleucine	180	180	960	192	189
Lysine HCl	620 (500)	620 (500)	963 (770)	189 (151)	330 (264)
Phenylalanine	290	290	640	138	175
Threonine	180	180	646	138	180
Tryptophan	60	60	320	48	45
Arginine HCl	—	270 (220)	830 (686.4)	147 (121.6)	165 (136.5)
Histidine HCl.$2H_2O$	—	130	370 (252.3)	—	143 (97.5)
Glycine	—	—	1490	—	236
Alanine	—	—	—	81	150
Aspartic acid	—	—	—	246	240
Glutamic acid	—	—	—	600	300
Proline	—	—	—	222	143
Serine	—	—	—	171	150
Tyrosine	—	—	—	165	5

Described below are experiments and clinical tests conducted with use of amino acid infusion solutions of this invention.

Experimental Example

Experimental animals are Donryu rats and Wistar rats weighing 150 to 160 g. Before the preparation of cancer-bearing animals, a catheter is set on each animal by the following method for performing continuous infusion under no restraints, followed by a three-day acclimation period.

Under nembutal narcosis, the cervicis skin of the rat is incised to expose the jugular vein to its branched portion on the subclavian vein. A catheter is inserted into the jugular vein until the forward end has reached the superior vena cave and then fixed. The other end of the catheter is passed under the skin and withdrawn from the body at a back portion. The catheter is then passed through a harness set in position and through a protective coil and connected by a swivel to a constant infusion pump. "BIO-CANNULA," (trade mark, infusion pump of BIO MEDICA LTD., Japan) is used for continuous infusion. During the following three-day acclimation period, PAN-AMIN (trade mark, amino acid infusion solution of Otsuka Pharm. Co., Ltd., Japan, hereinafter abbreviated as "PA") of the following composition is continuously given to the rat at a rate of 1.5 ml/hr, with free access to water and a protein-free diet of the following composition.

Composition of PA (in mg/100 ml)

Leucine	410
Valine	200
Isoleucine	180
Lysine HCl	620
Phenylalanine	290
Threonine	180
Tryptophan	60
Arginine HCl	270
Histidine HCl.$2H_2O$	130
Methionine	240
Glycine	340

Composition of the protein-free diet

α-Starch	47.83 g
Sucrose	23.92 g
Vitamine mixture [1]	1.0 g
Salt mixture [2]	5.0 g
Corn oil	5.0 g
Cellulose	2.0 g
"Chocola A" [3]	0.05 ml
Choline chloride	0.20 ml

The vitamin mixture [1] and the salt mixture [2] given above have the following compositions. "Chocola A," [3] trade mark, product of Eisai Co., Ltd., Japan, is palmitic acid ester of vitamin A containing 30,000 international units/ml of vitamine A (20 mg/ml of retinol palmitate).

Composition of the vitamin mixture (in w/v %)

Thiamine HCl	0.059
Riboflavin	0.059
Nicotinic acid	0.294
Calcium pantothenate	0.235
Pyridoxine HCl	0.029
Menadione	0.006
Biotin	0.001
Folic acid	0.002
Vitamin B_{12}	0.0002
Inositol	1.176
Ascorbic acid	0.588
Lactic acid	97.551

Composition of the salt mixture (in w/v %)

$CaCO_3$	29.29
$CaHPO_4.2H_2O$	0.43
KH_2PO_4	34.31
NaCl	25.06
$MgSO_4.7H_2O$	9.98
$Fe(C_6H_5O_7).6H_2O$	0.623
$CuSO_4.5H_2O$	0.156
$MnSO_4.H_2O$	0.121
$ZnCl_2$	0.02
$(NH_4)_6Mo_7O_4.4H_2O$	0.0025
KI	0.0005

1. Experiment on inhibition of solid cancers

Cancer-bearing animals are prepared after the termination of the acclimation period by transplant-

ing 2.7 x 10^7 cells/ml of Yoshida sarcoma and 9 x 10^6 cells/ml of AH 130 in Donryu rats, and 1 x 10^7 cells/ml of Walker sarcoma and Rhodamin sarcoma in an amount of 0.2 ml as cancer brei in Wistar rats. The cancers were transplanted in the left inguinal subcutanea of the animals. As shown in Table 1, the rats bearing cancer cells of the same kind and those bearing no cancer cells are divided into 12 groups; namely groups A-1 and A-4 given only the amino acid infusion solution of the invention (prepared in Example 1, hereinafter referred to as "AO-30"), groups A-2 and A-5 given both AO-30 and Mitomycin-C (hereinafter referred to as "MMC") and groups A-3 and A-6 given AO-30, MMC and a diet, and, as controls, groups P-1 and P-4 given only PA, groups P-2 and P-5 given both PA and MMC and groups P-3 and P-6 given PA, MMC and a diet conjointly. Each of the groups consists of 6 rats. AO-30 and PA are administered continuously at a rate of 1.5 ml/hr. MMC is intraperitoneally given at a dose of 0.1 mg/kg/day, starting 24 hours after implantation of the cancer. The diet is the protein-free diet stated above.

In Table 1, the mark "+" indicates that the rats are implanted with cancer, or given MMC or diet. The mark "−" indicates no implantation or no administration of MMC or diet.

Table 1

Group	*Implantation of cancer*	*MMC*	*Diet*
Control			
P-1	−	−	−
P-2	−	+	−
P-3	−	+	+
P-4	+	−	−
P-5	+	+	−
P-6	+	+	+
Invention			
A-1	−	−	−
A-2	−	+	−
A-3	−	+	+
A-4	+	−	−
A-5	+	+	−
A-6	+	+	+

The Yoshida sarcoma and AH 130 are removed from the rats on 12th day after transplant, and the Walker sarcoma and Rhodamin sarcoma on 15th day, and the cancers are weighed. Tables 2 to 5 show the results. The average weight of cancers, C, in the cancer-bearing group P-4 receiving PA alone is calculated. The average weight of cancer, T, in each of the cancer-bearing groups P-5, P-6 and A-4 to A-6 is also calculated. Tables 2 to 5 show the T/C ratio obtained. The results achieved are evaluated as effective when the T/C ratio is less than 0.50, as slightly effective when the ratio is 0.50 to 0.70, and as ineffective if the ratio is higher than 0.70.

The average weight of cancer listed in Tables 2 to 5 is the average of the maximum and minimum weights of the cancer in the 6 rats of the group concerned. The value including "+" is the maximum weight, and the value with "−" is the minimum.

Table 2 (Yoshida sarcoma)

Group	*Weight of cancer (mg)*	*T/C*
P-1	—	—
P-2	—	—
P-3	—	—
P-4	2689 ± 588	—
P-5	1860 ± 814	0.69
P-6	1865 ± 678	0.69
A-1	—	—
A-2	—	—
A-3	—	—
A-4	1720 ± 960	0.64
A-5	1135 ± 265	0.42
A-6	1126 ± 324	0.42

Table 2 reveals that the administration of the amino acid infusion solution, AO-30, of the invention singly (group A-4) achieves a reduction in the cancer weight as much as at least about 1/3 the cancer weight of the group receiving the known PA singly, thus indicating that AO-30 has a cancer inhibiting effect. Furthermore, the T/C ratio of group A-4, which is 0.64, is comparable or superior to those achieved by the administration of MMC (group P-5) and the use of both MMC and diet (group P-6). Group A-5 with AO-30 and MMC, and group A-6 with AO-30, MMC and diet exhibit effective results of 0.42 in terms of T/C ratio. This indicates that the conjoint use of AO-30 and MMC enhances the effect achieved by the single use thereof.

Table 3 (Walker sarcoma)

Group	*Weight of cancer (mg)*	*T/C*
P-1	—	—
P-2	—	—
P-3	—	—
P-4	5010 ± 1311	—
P-5	2783 ± 1001	0.56
P-6	2712 ± 873	0.54
A-1	—	—
A-2	—	—
A-3	—	—
A-4	1816 ± 878	0.36
A-5	1198 ± 522	0.24
A-6	1262 ± 375	0.25

Table 3 also reveals that the use of AO-30 (group A-4) leads to a reduction in the cancer weight corresponding to about 1/3 the cancer weight with use of PA (group P-4), thus showing that AO-30, even if used singly, is effective in inhibiting the cancer. The table further indicates that AO-30, when used conjointly with MMC or with both MMC and diet, produces more effective results.

Table 4 (AH 130)

Group	*Weight of cancer (mg)*	*T/C*
P-1	—	—
P-2	—	—
P-3	—	—
P-4	8005 ± 2891	—
P-5	4883 ± 1460	0.61
P-6	5046 ± 1100	0.63
A-1	—	—
A-2	—	—
A-3	—	—
A-4	4642 ± 910	0.58
A-5	2275 ± 1518	0.28
A-6	2300 ± 1005	0.29

Table 4, like Tables 2 and 3, similarly reveals that the amino acid solution of this invention produces effective results.

Table 5 (Rhodamin sarcoma)

Group	*Weight of cancer (mg)*	*T/C*
P-1	—	—
P-2	—	—
P-3	—	—
P-4	1007 ± 508	—
P-5	567 ± 416	0.56
P-6	500 ± 143	0.50
A-1	—	—
A-2	—	—
A-3	—	—
A-4	513 ± 171	0.51
A-5	268 ± 82	0.27
A-6	294 ± 46	0.29

Table 5, like Tables 2 to 4, similarly reveals the effectiveness of the amino acid infusion solution of the invention. The foregoing tables indicate that the amino acid infusion solution of the invention, unlike the conventional amino acid infusion solutions containing methionine, has outstanding inhibitory activity on various cancer cells.

2. Experiment on increase in life-span

Cancer-bearing animals are prepared by intraperitoneally giving 1.7×10^5 cells/ml of Yoshida sarcoma or 1.1×10^6 cells/ml of AH 130 to Donryu rats, and 1.0×10^5 cells/ml of Walker sarcoma to Wistar rats. In this experiment, an infusion solution of AO-30 (or PA for controls), glucose, electrolytes and vitamins is administered by so-called method of total parenteral nutrition (hereinafter referred to "TPN method"). The composition of the infusion solution is listed below.

Composition of the infusion solution

	Invention	*Control*
Amino acid	AO-30 16.1 g/l	PA 175 g/l
Glucose	200 g/l	200 g/l
Na^+	53 mEq/l	53 mEq/l
K^+	25 mEq/l	25 mEq/l
CL^-	53 mEq/l	53 mEq/l
HPO_4^{2-}	25 mEq/l	25 mEq/l
$CH_3CH(OH)COO^-$	48 mEq/l	48 mEq/l
Vitamin B_1	0.1 mg/rat/day	0.1 mg/rat/day
Vitamin B_2	0.01 mg/rat/day	0.01 mg/rat/day
Vitamin B_6	0.02 mg/rat/day	0.02 mg/rat/day
Vitamin C	0.5 mg/rat/day	0.5 mg/rat/day
Nicotinic acid	0.2 mg/rat/day	0.2 mg/rat/day
Panthenol	0.02 mg/rat/day	0.02 mg/rat/day
Calorific value	206 Cal/kg/day	208 Cal/kg/day
Dose	240 ml/kg/day	240 mg/kg/day
NPC/N*	337	317
Rate of infusion	1.5 ml/150 g body/hr	1.5 ml/150 g body/hr

NPC/N* means None Protein Calories/Nitrogen.

As shown in Table 6 below, the rats bearing the same cancer are divided into four groups, each ten rats, of: group A-1' given AO-30 and group A-2' given both AO-30 and MMC, and, as controls, group P-1' given PA and group P-2' receiving both PA and MMC. MMC is intraperitoneally infused at a dose of 0.1 mg/kg/day.

In Table 6, the mark "+" indicates the group given the inoculation or MMC, and the mark "−" the group given no inoculation or MMC.

Table 6

Group	*Inoculation of cancer*	*MMC infusion*
Control		
P-1'	+	−
P-2'	+	+
Invention		
A-1'	+	−
A-2'	+	+

The experimental animals are observed to determine the life-span for 30 days after inoculation. The mean survival time (hereinafter referred to as "MST") is calculated from the following equation.

$$MST = \frac{\Sigma (t \cdot f)}{n}$$

in which n: number of animals observed

f: number of animals died on t-th day

t: number of days of survival after transplant

The effect on increase in survival time is evaluated based on the T/C ratio, namely the ratio of the mean survival time C of group P-1' receiving PA as an amino acid infusion solution to the mean survival time T of each of the other cancer-bearing groups. The result is effective if the T/C ratio is higher than 1.25 but is ineffective if the ratio is lower than 1.25. Table 7 shows the results achieved on the cancers.

Table 7

Cancer	Group	MST (days)	T/C
Yoshida sarcoma	P-1'	11.9	—
	P-2'	15.9	1.34
	A-1'	15.0	1.26
	A-2'	19.9	1.67
AH 130	P-1'	13.6	—
	P-2'	>21.6	1.59
	A-1'	18.0	1.32
	A-2'	>25.1	1.85
Walker sarcoma	P-1'	14.7	—
	P-2'	>22.7	1.54
	A-1'	>22.4	1.52
	A-2'	>26.9	1.82

Table 7 indicates that the infusion solution of this invention used for any of the cancers produces 1.3 to 1.5 times the increase in life-span afforded by the PA infusion solution. The present solution further enhances the increase in life-span achieved by MMC when used in combination with MMC (group A-2').

Although not listed in Table 7, groups P-2' and A-2' inoculated with AH 130 attain survival ratios of 40% and 60% respectively 30 days after the inoculation. Group P-2' with Walker sarcoma has a survival ratio of 20%, whereas group A-2' with the same cancer has a survival ratio of as high as 50%.

The results described above show that the amino acid infusion solution of this invention which is free from methionine, when continuously given singly for a period of time, acts very effectively on Yoshida sarcoma, Walker sarcoma, AH 130 and Rhodamin sarcoma to inhibit the growth of the cancers and that the infusion solution exhibits still enhanced activity when used in combination with an anti-cancer agent such as MMC. Additionally the infusion solution of the invention, when given continuously as a sole nitrogen source by the TPN method, achieves a remarkable increase in life-span of the tested animals inoculated with Yoshida sarcoma, AH 130 and Walker sarcoma while enhancing the effect of MMC when used conjointly therewith.

Clinical Example 1

The patient was a 54-year-old man suffering from peritonitis carcinomatosa 2 years after total gastrectomy. The patient received celiotomy again, which nevertheless ceased to be mere abdominal surgery without any remedial procedure. The patient complained of severe vomitting due to carcinomatous constriction in the intestine and was seriously enfeebled. The amino acid infusion solution AO-30 prepared in Example 1 according to the invention was given to the patient by the TPN method daily at a dose of 500 ml/day for 4 weeks. Additionally the patient was given MMC, 5 - fluorouracil (hereinafter referred to as "5FU") and neocarzinostatin (hereinafter referred to as "NCS") individually in the following manner. MMC was intravenously given at a dose of 10 mg/cm² cancer area once a day, for the first 4 days and for 4 days after an interval of 2 weeks. 5FU was intravenously given at a dose of 10 mg/kg body weight once a day for the first 5 days and for 5 days following a 2-week interval. NCS was intravenously given at a dose of 2000 units once every day for the 4-week period. Four weeks after the start of infusion, the patient became able to ingest food and was restored to health and discharged.

Clinical Example 2

The patient was a 39-year-old man who was rehospitalized due to spread of cancer to the liver with jaundice one year after total gastrectomy. He had hepatoma, phlebismus in the abdominal wall, ascites and edema in the lower half of the body and was in a critical condition. As in Clinical Example 1, the patient was infused with the amino acid infusion solution AO-30 prepared in Example 1 by the TPN method and also given MMC, 5FU and NCS. The solution and the anti-cancer agents were given all at the same doses and in the same manner as in Clinical Example 1, except that the amino acid solution and NCS were given daily for 5 weeks. Five weeks after the start of infusion, the hepatoma and phlebismus disappeared with the other symptoms also alleviated, but the patient died of intestinal bleeding. The lesions were found by biopsy to have been extensively destroyed histologically.

CLAIMS

1. An amino acid solution for a patient with a cancer comprising essential amino acid, characterized in that the solution does not contain methionine which is a kind of essential amino acid.

2. An amino acid solution as defined in claim 1 which comprises:
1.4-14.0 g of leucine,
1.4-10.0 g of valine,
1.6-10.0 g of isoleucine,
1.5-14.9 g of lysine,
1.0- 9.4 g of phenylalanine,
1.0- 6.7 g of threonine, and
0.4- 4.0 g of tryptophan
per liter of the solution, but contains no methionine.

3. An amino acid solution as defined in claim 2 which further contains at least one nonessential amino acid selected from the group consisting of arginine, histidine, glycine, alanine, aspartic acid, glutamic acid, proline, serine, tyrosine and ornithine.

4. An amino acid solution as defined in claim 1 which comprises:
1.7-14.0 g of leucine,
1.7- 9.5 g of valine,
1.8- 9.6 g of isoleucine,
1.5-14.7 g of lysine,
1.0- 6.4 g of phenylalanine,
1.3- 6.7 g of threonine,
0.4- 3.5 g of tryptophan,
1.0-13.2 g of arginine,
0.9- 3.0 g of histidine,
2.3-15.0 g of glycine,
0- 4.8 g of alanine,
0- 2.5 g of aspartic acid,
0- 6.0 g of glutamic acid,
0- 2.3 g of proline,
0- 1.8 g of serine,
0- 1.7 g of tyrosine, and
0- 5.0 g of ornithine
per liter of the solution, but contains no methionine.

5. An amino acid solution as defined in claim 1 which comprises:

4.1 g of leucine,
2.0 g of valine,
1.8 g of isoleucine,
5.0 g of lysine,
2.9 g of phenylalanine,
1.8 g of threonine,
0.6 g of tryptophan,
2.2 g of arginine,
0.9 g of histidine, and
3.4 g of glycine

per liter of the solution, but contains no methionine.

6. A method of nourishing a patient with a cancer characterized by giving the patient the amino acid solution defined in claim 1.

7. A method as defined in claim 6 which is performed with conjoint administration of an anti-cancer agent.

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